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(57) Abstract

The replacement of chlorofluorohydrocarbon propellants in medical aerosols is of the utmost importance to the pharmaceutical industry. A number of formulations have been investigated. The present invention provides a medical aerosol formulation comprising a particular medicament, a fluorocarbon propellant and 6 to 25 % w/w of the total formulation of a polar co-solvent, such formulation being substantially free of surfactant. Cannisters suitable for delivering such a pharmaceutical formulation are also provided.

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AEROSOL FORMULATIONS

This invention relates to pharmaceutical formulations for inhalation aerosols. The Montreal Protocol on ozone depleting gases has made the reformulation of existing pharmaceutical aerosols for inhalation treatment containing chlorofluorohydrocarbon propellants, a matter of urgency for the pharmaceutical industry.

A number of hydrofluorocarbons (HFCs) have been the subject to toxicological testing and two in particular P134a (1,1,1,2-tetrafluoroethane) and P227 (1,1,1,2,3,3,3-heptafluoropropane) have been identified as safe for use in pharmaceutical aerosols.

A number of patent applications have been submitted in this field, the first being EP 372777, which discloses the use of four component mixtures, comprising a medicament, a surfactant, P134a and a co-solvent of higher polarity than the P134a, in the form of a solution or a suspension.

As inhalation aerosols are meant for administration to the lung, it has long been accepted that such formulations should contain as few ingredients as possible, to avoid putting unnecessary materials into the lung.

Historically, despite EP 372777, solution aerosols contained only medicament, propellant or propellant mixtures and, if necessary, co-solvent, usually ethanol, eg US 2868691. The use of a surfactant was normally unnecessary for solution aerosols. However, historically medicinal suspension aerosols have contained a surfactant eg US 3014844, as it was considered that the use of a surfactant was necessary to prevent agglomeration of particles, to prevent adhesion to the sides of the canister, and to aid valve lubrication and prevent valve sticking.

However it was disclosed in EP 616525 that it is possible to prepare medicament suspensions in a hydrofluorocarbon without the need for a surfactant, if a polar co-solvent was added. The normal co-solvent ethanol, has well established

physiological actions and being a pure absorbable liquid eliminates any possibility of residues remaining in the lung. Irritation or possible toxicity from the surfactant, many of which are mixtures of similar compounds, are avoided.

EP 616525 specifically limits the polar co-solvent level to 0.01 to 5% w/w and in particular states (page 3, line 55) that the preferred level is about 0.1% w/w.

According to a first aspect of the present invention there is provided a medicinal aerosol formulation comprising a particulate medicament, a fluorocarbon propellant and 6% to 25% w/w of the total formulation of a polar co-solvent, such formulation being substantially free of surfactant.

According to a second aspect of the present invention there is provided a medicinal aerosol formulation, comprising one or more particulate medicaments, one or more fluorocarbon or hydrocarbon or aliphatic gas propellants and 6% to 25% w/w of a polar co-solvent.

According to a third aspect of the present invention there is provided a canister suitable for delivering a pharmaceutical aerosol formulation, which comprises a container capable of withstanding the vapour pressure of the propellant used, which container is closed with a metering valve and contains a pharmaceutical aerosol formulation which comprises particulate medicament, a propellant consisting all or part of fluorocarbon and 6% to 25% of a polar co-solvent, which is substantially free of surfactant.

It has now been surprisingly found that higher levels of alcohol have beneficial results. Levels of 6% or more of ethanol produce satisfactory suspensions, which do not agglomerate on standing, and on reshaking produce finely dispersed medicament. It is believed that the higher levels of alcohol reduce the degree of deposition on the inside of the can. This is a very desirable feature. In addition, the use of these larger percentages of ethanol enables a much cheaper production process.

Medicinal aerosols can be filled either with one dose of liquid containing all of the ingredients mixed together or by

a two dose process where the first dose contains the medicament and all other ingredients, including co-solvents, surfactants, if any, ancillary compounds eg flavours, if any, and some times some of the propellant followed by a second dose of pure propellant. This two dose fill has major cost advantages in that the volume of mix for a fixed number of cans is significantly smaller enabling the use of smaller mixing vessels. In particular, with the use of the new HFC propellants, which have lower boiling points than the old CFC propellants, the use of a one dose fill may involve the use of cooled pressurised vessels to prevent evaporation of the propellant gas during mixing and filling. With the new formulations with added extra co-solvent a first mix of just medicament suspended in the co-solvent can be used, followed by a second dose of pure propellant. This means that the propellant can be dosed directly from a holding tank into the can without any need to mix and store with the other ingredients. For example a mix weight of 1g of medicament and co-solvent can be followed by 7.5g of propellant. In this way the volume to be mixed is reduced from 8.5g to 1g. All the examples in EP 616525 are of laboratory scale, where the handling problems are much easier, but all the formulations described are such that it would not be practicable to fill in two doses without mixing the propellant, as is the case with the present disclosure.

The description of the filling method given on page 5 lines 2-13 indicates that only a one dose filling method is envisaged.

In all cases of the present invention the medicament consists of a particle size suitable for inhalation into the lung and will thus be less than 100 microns, desirably less than 20 microns and preferably in the range of 1-10 microns, normally with a mean particle size 1-5 microns.

Medicaments which may be administered in aerosol formulations according to the invention include any drug useful in inhalation therapy which may be presented in a form which is substantially completely insoluble in the selected propellant.

Appropriate medicaments may thus be selected from, for example, analgesics, eg codeine, dihydromophine, ergotamine, fentanyl or morphine; anginal preparations, eg diltiazem; antiallergics, eg cromoglycate, ketotifen or nedocromil; anti-infectives, eg cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine; antihistamines, eg methapyrilene; anti-inflammatories, eg beclomethasone, flunisolide, budesonide, tipredane, triamcinolone acetonide or fluticasone; antitussives, eg noscapine; bronchodilators, eg ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, salbutamol, salmeterol, terbutaline, isoetharine, tolubuterol, orciprenaline; diuretics, eg amiloride; anticholinergics, eg ipratropium, atropine or oxitropium; hormones, eg cortisone, hydrocortisone or prednisolone; xanthines, eg aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; and therapeutic proteins and peptides, eg insulin or glucagon. It will be clear to a person skilled in the art that, where appropriate, the medicaments may be used in the form of salts (eg as alkali metal or amine salts or as acid addition salts) or as esters (eg lower alkyl esters) or as solvates (eg hydrates) to optimise the activity and/or stability of the medicament and/or to minimise the solubility of the medicament in the propellant.

Preferred are those compounds which are also substantially insoluble in the co-solvent. Particularly preferred as medicament is salbutamol either as base or as a salt and especially salbutamol sulphate.

Co-solvents may be selected from polar alcohols and polyols, particularly C_2-C_6 aliphatic alcohols and polyols, such as propylene glycol, and preferably ethanol. Levels of co-solvent will be between 6% and 25% w/w of the total canister content, preferably between 10-15% w/w of canister content.

The propellant may be a hydrofluorocarbon, particularly P134a or P227. Other hydrofluorocarbons or hydrocarbons or aliphatic gases (eg Dimethylether) may be added to modify the

propellant characteristics as required.

The product is preferentially produced by weighing the active medicament and suspending it in the co-solvent. The appropriate amount of suspension is then dosed into the can, followed by a second dose of propellant or propellant mix. However, a one shot fill or any other equivalent method may be employed.

The normal medicinal product on the market has an actuator with spray orifice diameter of about 480 microns. However, with the larger percentages of ethanol envisaged in this invention, it is desirable that the co-solvent evaporates from the particles as rapidly as possible.

This is achieved by reducing the aperture to between 100-300 microns, which for the same dosage or drug, gives more rapid evaporation of the co-solvent. A particularly preferred embodiment of the invention is a combination of a level 10-15% co-solvent (normally ethanol) with a stem aperture of 150-250 microns.

The invention is further described by means of example but not in any limitative sense.

Example

Salbutamol Sulphate	0.03g
Ethanol	0.97g
Tetrafluoroethane (P134a)	7.5g

The salbutamol sulphate previously micronised to give over 90% of particles below 10 microns was weighed out and added to the ethanol. The suspension was mixed until is was smooth and uniform and then filled into the aerosol canister. The metering valve assembly was crimped (preferably vacuum crimped) on the canister and then the P134a was filled through the valve. The valve capacity is such as to deliver 100 micrograms of salbutamol, as salbutamol sulphate per actuation.

A particularly preferred use of such a canister is in a patient breath operated device rather than the normal hand

operated device. Such devices are available commercially such as those under the trade mark "Easi-Breathe".

Claims:

1. A medicinal aerosol formulation comprising a particulate medicament, a fluorocarbon propellant and 6% to 25% w/w of the total formulation of a polar co-solvent, such formulation being substantially free of surfactant.

2. A medicinal aerosol formulation, comprising one or more particulate medicaments, one or more fluorocarbon or hydrocarbon or aliphatic gas propellants and 6% to 25% w/w of a polar co-solvent.

3. A formulation as claimed in claim 1 or claim 2, wherein the medicament is an anti-allergic, a bronchodilator or an anti-inflammatory steroid.

4. A formulation as claimed in claim 3, where the medicament is ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropandamine, pirbuterol, reproterol, rimiterol terbutaline, isoetharine, orciprenaline, salbutamol, salmeterol, sodium cromoglycate, fluticasone, beclomethasone or similar molecule and any physiologically acceptable salt, solvate or ester of such compound.

5. A formulation, as claimed in claims 1-3, where the medicament is a salt of salbutamol.

6. A formulation, as claimed in claims 1-3, where the medicament is a salt of formoterol (sometimes called eformoterol).

7. A formulation according to any of claims 1 to 5, wherein the propellant is 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoro-n-propane.

8. A formulation according to any of claims 1 to 5,

where the co-solvent level is 10-15%.

9. A formulation according to any of claims 1-5, wherein the polar co-solvent is ethanol.

10. A canister suitable for delivering a pharmaceutical aerosol formulation, which comprises a container capable of withstanding the vapour pressure of the propellant used, which container is closed with a metering valve and contains a pharmaceutical aerosol formulation which comprises particulate medicament, a propellant consisting all or part of fluorocarbon and 6% to 25% of a polar co-solvent, which is substantially free of surfactant.

11. A canister according to claim 9, fitted into an adaptor with an aperture of 100-300 microns.

12. A product according to claims 9 and 10 where the medicament is as per claim 4.

13. A product according to claims 9-11, where the medicament is a salt of salbutamol.

14. A product according to claims 9-11, where the medicament is a salt of formoterol.

15. A canister according to claims 9 and 10, which is actuated by a breath operated device.

16. A product according to claim 15, where the medicament is a salt of salbutamol.

17. A product according to claim 15, where the medicament is a salt of formoterol.

INTERNATIONAL SEARCH REPORT

Interm al Application No PCT/GB 97/01502

A. CLASSIFICATION OF SUBJECT MATTER

A 61 K 9/12

According to International Patent Classification (IPC) or to both national classification and IPC 6

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A 61 K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO, A, 93/11 745 (GLAXO GROUP LIMITED) 24 June 1993 (24.06.93), abstract; claims 1-15. --	1-5, 7-10
A	WO, A, 93/11 743 (GLAXO GROUP LIMITED) 24 June 1993 (24.06.93), abstract; claims 1-21. --	1-5, 7-10
A	WO, A, 94/03 153 (GLAXO GROUP LIMITED) 17 February 1994 (17.02.94), abstract; claims 1-12. --	1-5, 7-10
A	WO, A, 94/13 262 (JAGER et al.) 23 June 1994 (23.06.94), abstract; claims 1-38,	1-5, 7-9

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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	especially claim 4.	

ANHANG

zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

ANNEX

to the International Search Report to the International Patent Application No.

ANNEXE

au rapport de recherche international relatif à la demande de brevet international n°

PCT/GB 97/01502 SAE 162218

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

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In Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
WO A1 9311745		AP A0 9200461 AP A 402 AT E 128350 AU A1 30850/93 AU A1 30851/93 AU A1 30852/93 AU B2 663904 AU B2 663905 AU B2 663906 BG A 98803 CN A 1075078 CN A 1075079 CZ A3 9401430 DE D0 69205177 DE T2 69205177 EP A1 616527 EP A1 616528 EP A1 616529 EP B1 616529 EP A2 756868 EP A3 756868 ES T3 2078210 GB A0 9202522 HU A0 9401742 HU A2 67544 HU A0 9500741 HU B2 211671 IL A0 104068 JP T2 7501811 JP T2 7502033 JP T2 7502034 NO A 942185 NO A0 942185 NZ A 246046 NZ A 246044 OA A 9926 SK A3 674/94 US A 5653962 US A 5658549 WO A1 9311743 WO A1 9311744 WO A2 9311745 GB A0 9114444 ZA A 9209610 GB A0 9126405 GB A0 9126378 ZA A 9209617	31-01-94 25-08-95 15-10-92 19-07-93 19-07-93 19-07-93 26-10-95 26-10-95 26-10-95 28-02-92 11-08-93 11-08-93 15-03-95 02-11-95 31-03-97 28-09-94 28-09-94 28-09-94 27-09-94 26-02-97 26-02-97 01-01-96 25-03-93 28-09-94 28-04-95 28-09-95 28-12-95 13-05-95 23-02-95 02-03-95 02-03-95 10-06-94 10-06-94 21-12-95 26-01-96 15-09-94 08-03-95 05-08-97 19-08-97 24-06-93 24-06-93 24-06-93 12-08-93 09-08-93 12-08-93 12-08-93 25-08-94
WO A1 9311743 24-06-93		AP A0 9200461 AP A 402 AT E 128350 AU A1 30850/93 AU A1 30851/93 AU A1 30852/93 AU B2 663904 AU B2 663905 AU B2 663906 BG A 98803 CN A 1075078 CN A 1075079 CZ A3 9401430 DE D0 69205177 DE T2 69205177 EP A1 616527 EP A1 616528 EP A1 616529 EP B1 616529 EP A2 756868 EP A3 756868 ES T3 2078210 GB A0 9202522	31-01-94 25-08-95 15-10-92 19-07-93 19-07-93 19-07-93 26-10-95 26-10-95 26-10-95 28-02-92 11-08-93 11-08-93 15-03-95 02-11-95 31-03-97 28-09-94 28-09-94 28-09-94 27-09-94 26-02-97 26-02-97 01-01-96 25-03-93

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			HU	A2	675544
			HU	A3	9500331
			HU	B2	211671
			IL	A0	104068
			JP	T2	7501811
			JP	T2	7502044
			JP	T2	7502034
			NO	A	942188
			NO	A0	942188
			NZ	A	246046
			NZ	A	246044
			OA	A	9926
			SK	A3	674/94
			US	A	5465762
			US	A	5458549
			WO	A1	9311744
			WO	A2	9311745
			GB	A0	9116478
			GB	A0	9126444
			ZA	A	9209618
WO A1	9403153	17-02-94	AU	B2	670616
			AU	A1	70363/96
			CN	A	1088436
			EP	A1	598101
			EP	A1	775484
			GB	A0	9216382
			JP	T2	7509477
			GB	A0	9216381
			ZA	A	9305477
WO A1	9413262	23-06-94	AU	A1	57405/94
			AU	A1	60486/94
			AU	B2	680277
			BG	A	99760
			CN	A	1095265
			CZ	A3	9501490
			EP	A1	673240
			FI	A	952842
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			NZ	A	259151
			PL	A1	309234
			SK	A3	760/95
			WO	A1	9413262
			ZA	A	9309195